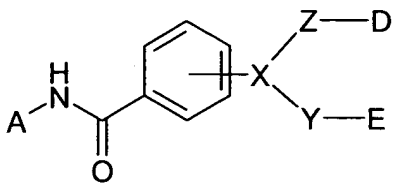
CLAIMS

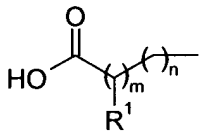
1. A compound of the general formula (I)



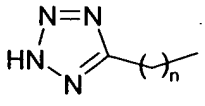
(I)

wherein

A is



or



,

m is 0 or 1,

n is 0, 1, 2 or 3,

with the proviso that m and n must not both be 0,

R^1 is hydrogen, fluoro or $-(CH_2)_o-OR^2$,

o is 0 or 1,

R^2 is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkanoyl , aryl or aryl-C_{1-6}-alkyl,

X is N, CH or C with a double bond to one substituent,

Z is $-CR^3R^4-$, $-(C=O)-(NR^5)-(C_{1-6}\text{-alkyl})_K-$, $-(C=O)-O-(C_{1-6}\text{-alkyl})_K-$, $-(C=O)-(C_{1-6}\text{-alkyl})_K-$, $-(C_{1-6}\text{-alkyl})_K(C=O)-O-$, $-(C=O)-O-(C_{2-6}\text{-alkenyl})_K-$, $-(C=O)-(C_{2-6}\text{-alkenyl})_K-$, $-(C_{1-6}\text{-alkenyl})_K(C=O)-O-$

wherein k is 0 or 1,

R^3, R^4 and R^5 are independently selected from hydrogen, C_{1-6}-alkyl or aryl,

Y is $-(C_{1-6}\text{-alkyl})_s\text{-}(C{=}O)\text{-}(C_{1-6}\text{-alkyl})_t\text{-}$, $-(C_{1-6}\text{-alkenyl})_s\text{-}(C{=}O)\text{-}(C_{1-6}\text{-alkyl})_t\text{-}$, $-C_{1-6}$-alkyl-, $-C_{2-6}$-alkenyl-, or $-CR^6R^7-$

wherein s and t independently are 0 or 1;

wherein R^6 , R^7 and R^8 independently are selected from hydrogen, C_{1-6}-alkyl and aryl;

D is aryl or heteroaryl, which may optionally be substituted with one or more substituents R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, wherein

R^{16}, R^{17}, R^{18} and R^{19} independently are

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$, $-SR^{22}$, $-NR^{22}S(O)_2R^{23}$, $-S(O)_2NR^{22}R^{23}$, $-S(O)NR^{22}R^{23}$, $-S(O)R^{22}$, $-S(O)_2R^{22}$, $-C(O)NR^{22}R^{23}$, $-OC(O)NR^{22}R^{23}$, $-NR^{22}C(O)R^{23}$, $-CH_2C(O)NR^{22}R^{23}$, $-OCH_2C(O)NR^{22}R^{23}$, $-CH_2OR^{22}$, $-CH_2NR^{22}R^{23}$, $-OC(O)R^{22}$, $-C(O)R^{22}$ or $-C(O)OR^{22}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -C(O)OR^{22}, -CN, -CF_3, -OCF_3, -NO_2, -OR^{22}, -$NR^{22}R^{23}$ and C_{1-6}-alkyl,

R^{22} and R^{23} independently are hydrogen, C_{1-6}-alkyl, aryl-C_{1-6}-alkyl or aryl, or R^{22} and R^{23} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{16} to R^{19} when placed in adjacent positions together may form a bridge –$(CR^{24}R^{25})_a$-O-$(CR^{26}R^{27})_c$-O-,

a is 0, 1 or 2,

c is 1 or 2,

R^{24}, R^{25}, R^{26} and R^{27} independently are hydrogen, C_{1-6}-alkyl or fluoro,

R^{20} and R^{21} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is

C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl, which may optionally be substituted with one or two substituents R^{28} and R^{29}, which are independently selected from

- hydrogen, halogen, -CN, -CF_3, -OR^{33}, -$NR^{33}R^{34}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heteroaryl and aryl,

  wherein the heteroaryl and aryl groups optionally may be substituted with one or more substituents selected from halogen, -CN, -CF_3, -NO_2, -OR^{33}, -$NR^{33}R^{34}$ and C_{1-6}-alkyl,

  R^{33} and R^{34} independently are hydrogen or C_{1-6}-alkyl,

or R^{33} and R^{34} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

aryl, heteroaryl, aryl-C_{2-6}-alkenyl or aryl-C_{2-6}-alkynyl, of which the cyclic moieties may optionally be substituted with one to three substitutents R^{30}, R^{31} and R^{32}, which are independently selected from

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$, $-S(O)R^{35}$, $-S(O)_2R^{35}$, $-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-OCH_2C(O)NR^{35}R^{36}$, $-C(O)R^{35}$ and $-C(O)OR^{35}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl and heteroaryl-C_{2-6}-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

  wherein R^{35} and R^{36} independently are hydrogen, C_{1-6}-alkyl or aryl,

  or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

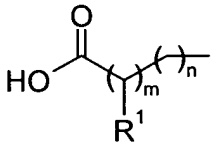
or two of the substituents R^{30}, R^{31} and R^{32} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-$(CH_2)_t$-$CR^{37}R^{38}$-$(CH_2)_l$-O-, -$(CH_2)_t$-$CR^{37}R^{38}$-$(CH_2)_l$- or -S-$(CH_2)_t$-$CR^{37}R^{38}$-$(CH_2)_l$-S-,

t and l independently are 0, 1, 2, 3, 4 or 5,

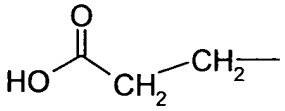
R^{37} and R^{38} independently are hydrogen or C_{1-6}-alkyl,

as well as any diastereomer or enantiomer or tautomeric form or mixture thereof, or a pharmaceutically acceptable salt thereof.

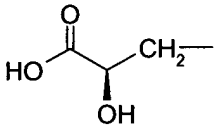
2. A compound according to claim 1, wherein A is



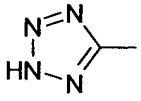
3. A compound according to claim 2, wherein A is



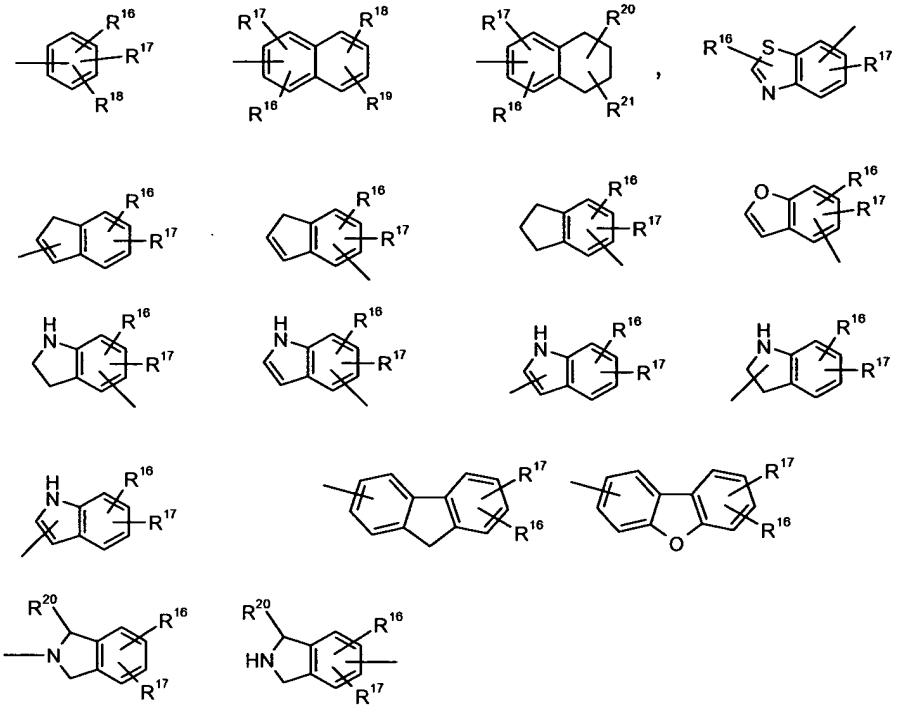
4. A compound according to claim 2, wherein A is



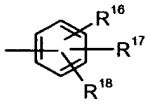
5. A compound according to claim 1, wherein A is



6. A compound according to claim 1, wherein D is



7. A compound according to claim 6, wherein D is



8. A compound according to claim 6, wherein R^{16}, R^{17} and R^{18} independently are

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$, $-SR^{22}$, $-NR^{22}S(O)_2R^{23}$, $-S(O)_2NR^{22}R^{23}$, $-S(O)NR^{22}R^{23}$, $-S(O)R^{22}$, $-S(O)_2R^{22}$, $-C(O)NR^{22}R^{23}$, $-OC(O)NR^{22}R^{23}$, $-NR^{22}C(O)R^{23}$, $-CH_2C(O)NR^{22}R^{23}$, $-OCH_2C(O)NR^{22}R^{23}$, $-CH_2OR^{22}$, $-CH_2NR^{22}R^{23}$, $-OC(O)R^{22}$, $-C(O)R^{22}$ or $-C(O)OR^{22}$,
- C_{1-6}-alkyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{22}$ and $-NR^{22}R^{23}$,
- C_{3-8}-cycloalkyl, which may optionally be substituted with one or more substituents selected from fluoro, $-C(O)OR^{24}$, -CN, $-CF_3$, $-OCF_3$, $-OR^{22}$, $-NR^{22}R^{23}$ and C_{1-6}-alkyl,
- aryl or aryloxy, which may optionally be substituted with one or more substituents selected from halogen, $-C(O)OR^{22}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{22}$, $-NR^{22}R^{23}$ and C_{1-6}-alkyl,

R^{22} and R^{23} independently are hydrogen, C_{1-6}-alkyl, aryl-C_{1-6}-alkyl or aryl, or R^{22} and R^{23} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

- or two of the groups R^{16} to R^{18} when placed in adjacent positions together may form a bridge $-(CR^{24}R^{25})_a-O-(CR^{26}R^{27})_c-O-$,

a is 0, 1 or 2,

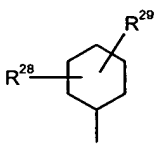
c is 1 or 2,

R^{24}, R^{25}, R^{26} and R^{27} independently are hydrogen, C_{1-6}-alkyl or fluoro.

9. A compound according to claim 8, wherein R^{16}, R^{17} and R^{18} independently are

- hydrogen, halogen, CN, $-CF_3$, $-OCF_3$, $-SCF_3$, -S(O) C_{1-6}-alkyl-, -C(O) C_{1-6}-alkyl-, C_{1-6}-alkyl, C_{1-6}-alkoxy, phenyl, cyclopentyl, cyclohexyl or phenoxy,
- or two of the groups R^{16} to R^{18} when placed in adjacent positions together may form a bridge $-O-(CF_2)_2-O-$, $-CF_2-O-CF_2-O-$ or $-O-CH_2-O-$.

10. A compound according to claim 1, wherein E is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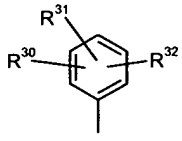
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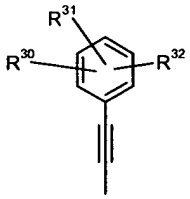
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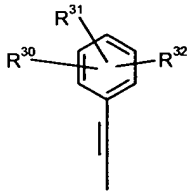
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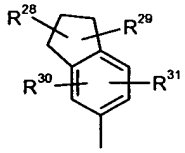
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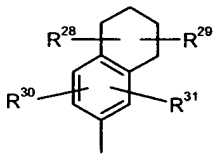
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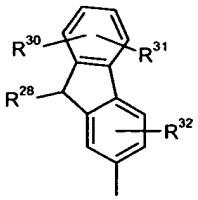
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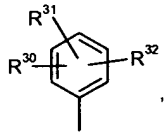
11. A compound according to claim 10, wherein E is



12. A compound according to claim 10, wherein R^{30}, R^{31} and R^{32} independently are

- hydrogen,
- halogen, $-OCF_3$, $-SCF_3$, $-OCHF_2$ or $-CF_3$,
- C_{1-6}-alkyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$ and $-NR^{35}R^{36}$,
- C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,
- aryl, heteroaryl, aryloxy or aryl-C_{1-6}-alkoxy, of which the aryl moieties may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-R^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

R^{35} and R^{36} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds.

13. A compound according to claim 12, wherein R^{30}, R^{31} and R^{32} independently are

- hydrogen,
- halogen, $-OCF_3$, $-OCHF_2$, $-SCF_3$, or $-CF_3$,
- C_{1-6}-alkyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$ and $-NR^{35}R^{36}$,
- cyclohexyl or cyclohex-1-enyl, which may optionally be substituted with one or more substituents selected from fluoro, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,
- phenyl which may optionally be substituted with one or more substitutents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,

- phenoxy or benzyloxy, of which the phenyl moieties may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$ and C_{1-6}-alkyl,
- thiadiazolyl,

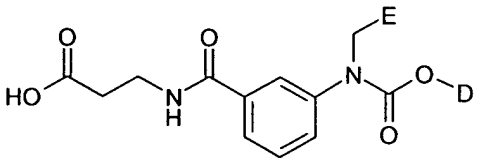
R^{35} and R^{36} independently are hydrogen or C_{1-6}-alkyl.

14. A compound according to claim 10, wherein R^{30} and R^{32} are both hydrogen, and R^{31} is different from hydrogen.

15. A compound according to claim 1, wherein Y is –C=O-, $–CH_2$-.

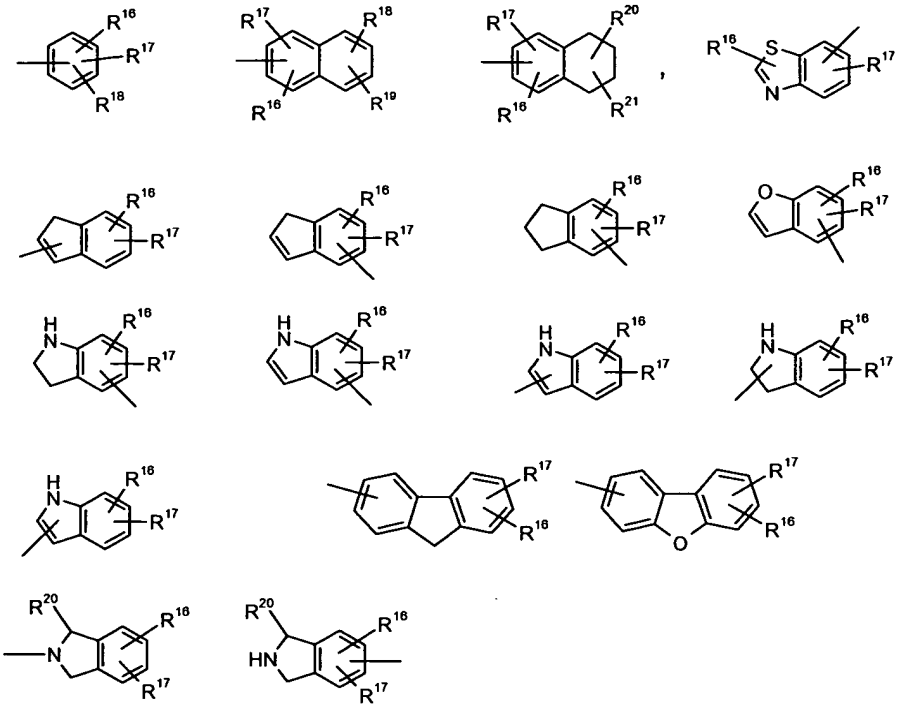
16. A compound according to claim 1, wherein Z is $–CH_2$-, -(C=O)-(NH), -(C=O)-O - or -(C=O)-CH_2-.

17. A compound of general formula (Ia);

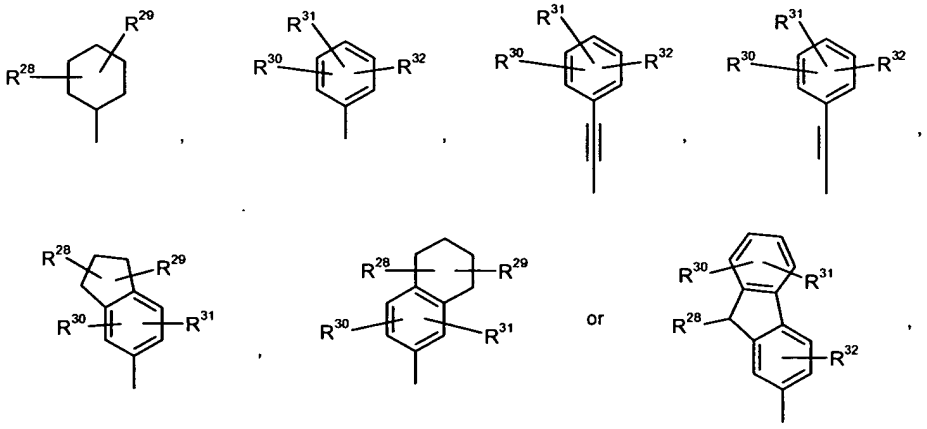


(Ia)

wherein D is selected from the following:

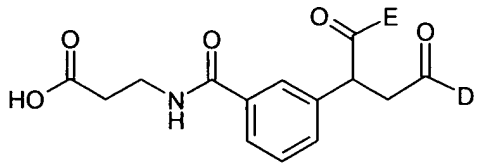


and wherein E is selected from the following:



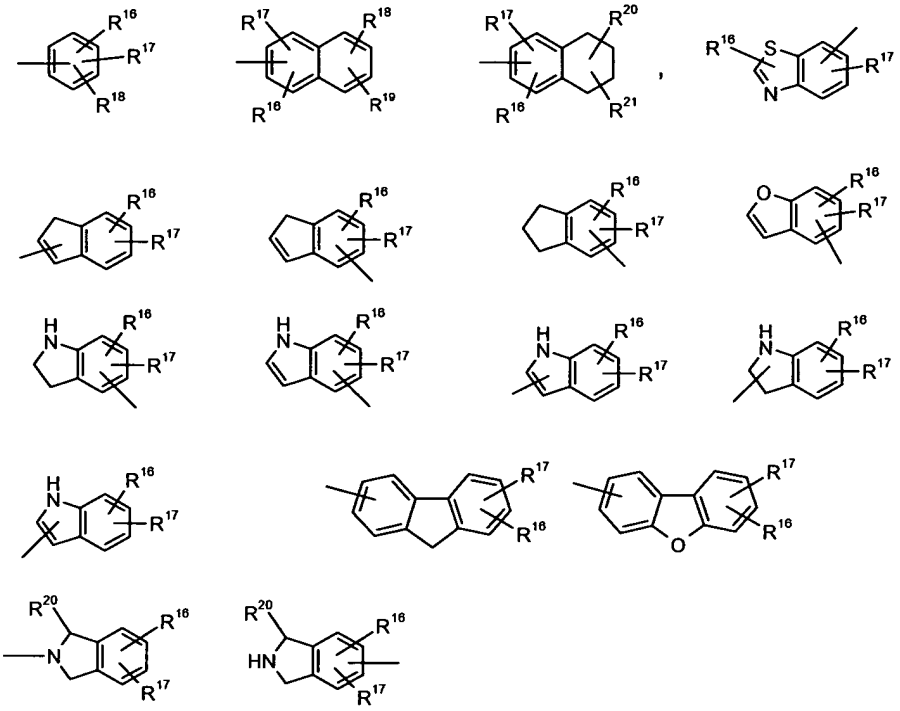
as well as any diastereomer or enantiomer or tautomeric form, or mixture thereof, or pharmaceutical acceptable salts thereof.

18. A compound of general formula (Ib);

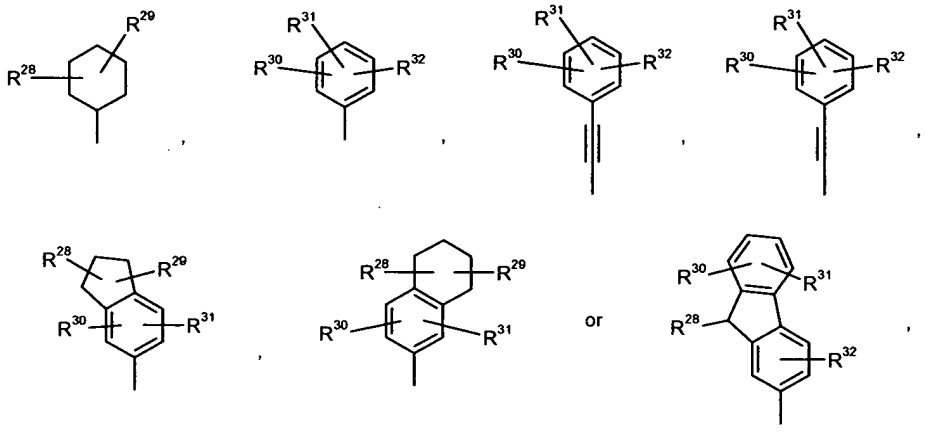


(Ib)

wherein D is selected from the following,

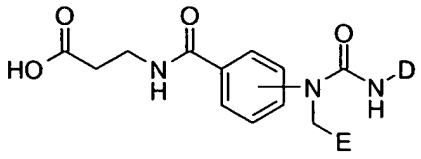


and wherein E is selected from the following:



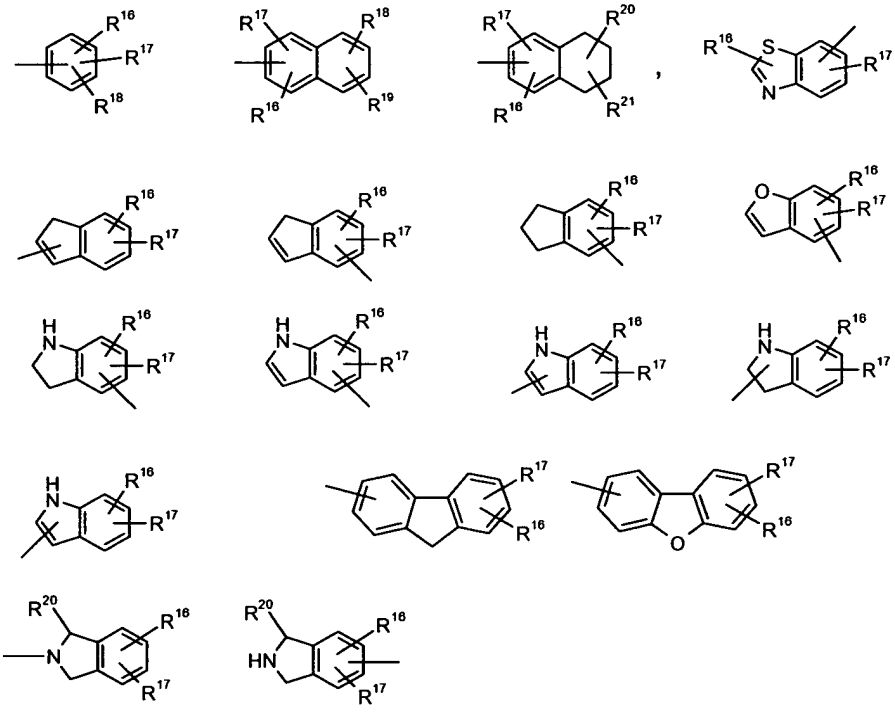
as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these or pharmaceutical acceptable salts thereof.

19. A compound of general formula (Ic)

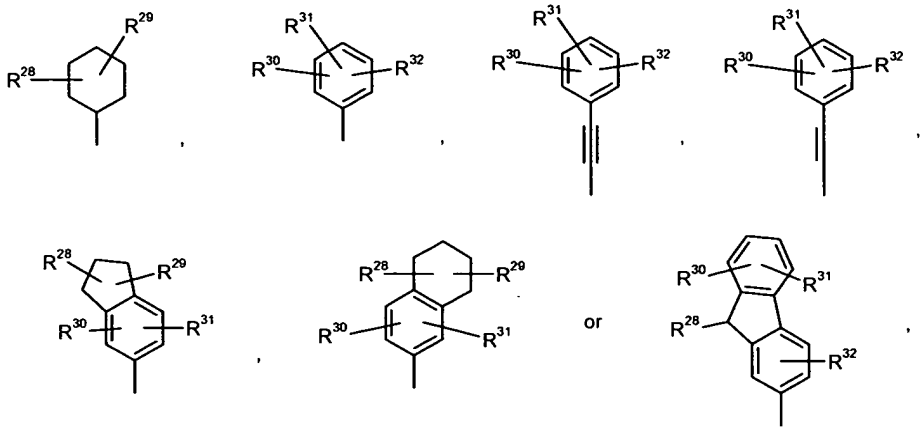


(Ic)

wherein D is selected from the following,

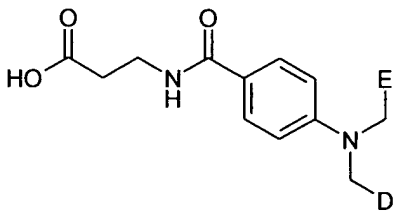


and wherein E is selected from the following,



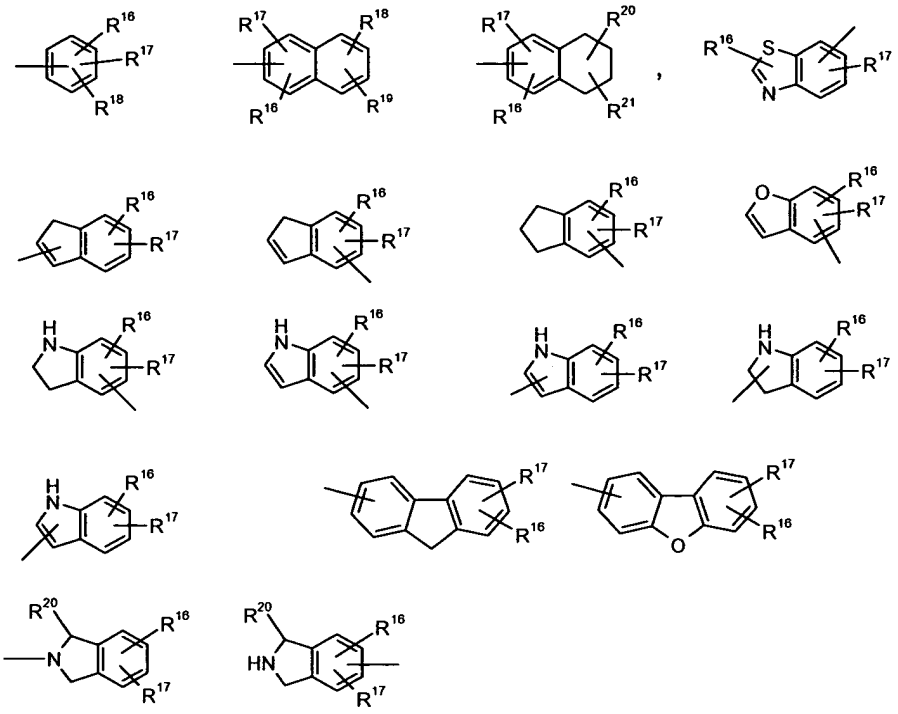
as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these or pharmaceutical acceptable salts thereof.

20. A compound of the general formula (Id):

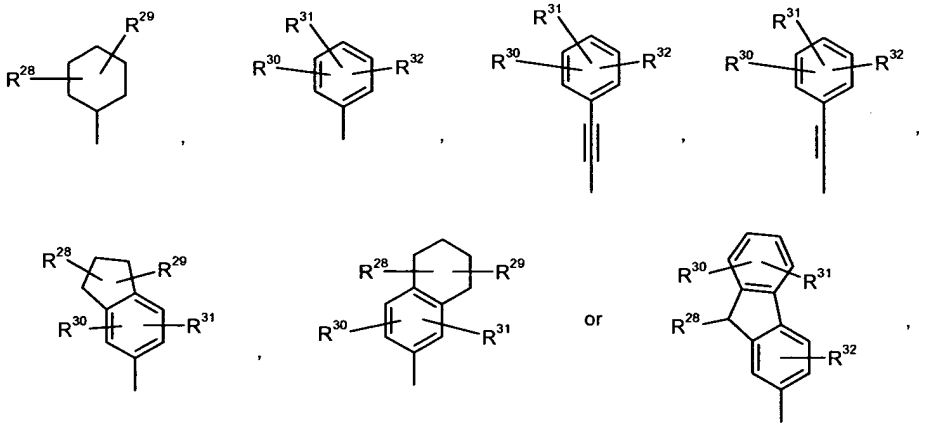


(Id)

wherein D is selected from the following:



and wherein E is selected from the following:



as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these or pharmaceutical acceptable salts thereof.

21. A compound according to claim 1, which has an IC_{50} value of no greater than 5 μM as determined by the Glucagon Binding Assay (I) or Glucagon Binding Assay (II) disclosed herein.

22. A compound according to claim 21, which has an IC_{50} value of less than 1 μM, preferably of less than 500 nM and even more preferred of less than 100 nM as determined by the Glucagon Binding Assay (I) or Glucagon Binding Assay (II) disclosed herein.

23. A compound according to claim 1, which is an agent useful for the treatment of an indication selected from the group consisting of hyperglycemia, IGT, type 2 diabetes, type 1 diabetes, dyslipidemia and obesity.

24. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to claim 1 together with one or more pharmaceutically acceptable carriers or excipients.

25. A pharmaceutical composition according to claim 24 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound.

26. A method of treating disorders or diseases, wherein a glucagon antagonistic action is beneficial, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

27. A method of treating glucagon-mediated disorders and diseases, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

28. A method of treating hyperglycemia, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

29. A method of lowering blood glucose in a mammal, comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of claim 1.

30. A method of treating IGT, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

31. A method of treating type two diabetes, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

32. A method of delaying or prevention of the progression from non-insulin requiring type 2 diabetes to insulin requiring type two diabetes in a subject, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

33. A method of delaying or prevention of the progression from IGT to type 2 diabetes in a subject, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

34. A method of treating type one diabetes, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

35. A method of treating obesity, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

36. A method of treating dyslipidemia, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

37. A method according to claim 26 wherein the subject is administered a further antidiabetic agent.

38. A method according to claim 26 wherein the subject is administered a further antiobesity agent.

39. A method according to claim 26 wherein the subject is administered a further antihyperlipidemic agent.

40. A method according to claim 26 wherein the subject is administered a further antihypertensive agent.

41. A method of treating disorders or diseases, wherein a glucagon antagonistic action is beneficial, comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition of claim 24.

42. The method according to claim 26, wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, preferably from about 0.1 mg to about 1000 mg and especially preferred from about 0.5 mg to about 500 mg per day.